APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,440	01/10/2002	Costas D. Maranas	P05468US1	1336

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EXAMINER
MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)
Office Action Summary	10/043,440	MARANAS ET AL.
	Examiner	Art Unit	
	Marjorie A. Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on <u>14 September 2004</u>.

2a)☒ This action is **FINAL.**   2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) <u>1-29</u> is/are pending in the application.

    4a) Of the above claim(s) <u>9,17 and 18</u> is/are withdrawn from consideration.

5)☒ Claim(s) <u>29</u> is/are allowed.

6)☒ Claim(s) <u>1- 8, 10-16, and 19-27</u> is/are rejected.

7)☒ Claim(s) <u>28</u> is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
    Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

Election/Restrictions

Claims 9 and 17-18 are again withdrawn from further consideration pursuant to

37 CFR 1.142(b) as being drawn to a nonelected species or Invention, there being no

allowable generic or linking claim. Election was made **without** traverse in the reply filed

on 4/1/04.

New claims 20-29 depend from or recite subject matter encompassed by Group

I, elected 4/1/04, and are therefore also considered elected.

An action on the merits of elected claims 1- 8, 10-16, and 19-29, as they read on

the elected specie, follows.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that

form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-5, 19-20, 22-23, 25-27 are rejected under 35 U.S.C. 102(a) as being

anticipated by EDWARDS et al. (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pages 1-

10).

EDWARDS teaches a method and system for modeling E. coli metabolism by

constructing a flux balance analysis model and applying constraints to the model, and

teaches that the model may be defined by cellular constraints (or barriers); specifically

include kinetic or gene regulatory constraints (pp. 2-3), thus anticipating claims 1, 3, 6,

19-20, 23, 25. EDWARDS teaches use of mixed-integer linear programming to calculate a desired metabolic outcome, specifically to calculate a minimal set of metabolic reactions to achieve particular growth rates (p. 3), thus anticipating claims 4-5, 12-15, and 26-27. EDWARDS teaches in silico examples of genetic engineering and calculation of a relationship between metabolic concentrations of cofactors and changes in reaction fluxes (pp. 4-5 and tables), thus anticipating claims 8 and 16. EDWARDS teaches incorporation of gene deletion data into his analysis (p. 6), thus anticipating claim 22.

Applicant's arguments filed 9/14/04 have been fully considered but they are not persuasive.

EDWARDS teaches a method and system for modeling E. coli metabolism using a flux balance analysis model which is subjected to constraints (p.2) and specifically teaches that regulatory or kinetic constraints may be applied to a feasible set of reactions (flux distributions) included in the model (p. 3), as set forth above. Applicant argues on pages 8-9 of the response the examiner has misconstrued the teaching of EDWARDS, as EDWARDS (a) does not actually teach qualitative kinetic constraints, and (b) that the kinetic constraints taught by EDWARDS are used to constrain the reactions in the model, not the model itself. In response, it is noted that the model taught by EDWARDS is clearly a flux balance analysis (FBA) model, as evidenced by the title "Flux Balance Analysis" on page 2, left column. Further, EDWARDS specifically teaches on pages 2-3 that a flux balance analysis IS a model which is subjected to at least mass balance constraints, thus applicant's arguments that

EDWARDS actually teaches two different models is moot. Further, on page 3, left column, EDWARDS teaches that a feasible set of flux distributions defines the metabolic network *subject to imposed cellular constraints*, thus teaching that the "feasible set" is necessarily included in his model. Given this teaching, application of the regulatory and/or kinetic constraints to EDWARDS' feasible set is inherently application of these constraints to his FBA model. The argument that EDWARDS only teaches quantitative, but not qualitative kinetic constraints, is also moot as EDWARDS does not specifically teach quantitative kinetic constraints, thus his kinetic constraints inherently encompass both qualitative and quantitative features. The instantly rejected claims do not recite "logic constraints," therefore arguments with regard to this limitation are moot. The argument is addressed below as it applies to claims rejected under 35 USC 103.

For these reasons, the examiner maintains that EDWARDS anticipates the claims, therefore the rejection of claims 1, 3-6, 8, 12-16, and 19 is maintained and new claims 20, 23, and 25-27 are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 6-8, 10-16, 21 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over EDWARDS et al. (IDS ref: BMC Bioinformatics (2000) vol. 1:1, pages 1-10) as applied to claims 1, 3-5, 19-20, 22-23, and 25-27 above, and further in view of SCHILLING et al. (IDS ref: PNAS (4/1998) vol. 95, pp. 4193-4198).

Claims 1, 6, 19-20, 23, and 25-27 recite methods and a system for modeling cellular metabolism of an organism by constructing a flux balance analysis model and applying constraints to the model. Claims 1, 3, 19 and 23 further limit the constraints to particular constraints. Claims 2, 6-7, 21, and 24 further limit the constraints to be logic constraints, specifically those which protect against violation of a kinetic or regulatory barrier. Claims 4-5, 14-15, and 26 further limit the methods to applying mixed-integer linear programming to solve for a desired metabolic outcome and solving for a desired metabolic outcome. Claims12 and 13 limit the method of claim 6 to further comprise a computational procedure to identify a minimal set of metabolic reactions and to identify a minimal set of reactions to support a selected growth rate. Claim 8 limits the method

of claim 6 to one wherein logic constraints are defined by a relationship between changes in reaction fluxes and metabolic concentrations. Claim 10 limits the logic constraints to be represented by binary variables.

EDWARDS teaches a method and system for modeling E. coli metabolism by constructing a flux balance analysis model and applying constraints to the model, as set forth above. EDWARDS teaches that his "feasible set" of reactions is subject to cellular constraints (p. 3), but does not specifically teach selecting constraints to protect against a violation of a kinetic or regulatory barrier. EDWARDS does not teach binary variables.

SCHILLING teaches flux balance analysis of metabolic reactions in cells using linear programming wherein only vectors (pathways) which are biochemically feasible are included (p. 4195). SCHILLING also teaches that his programming includes binary variables (p. 4195). SCHILLING teaches that all reactions have a value of 1 (p. 4195), therefore a value of 0 necessarily represents the absence of a reaction.

It would have been obvious to one of ordinary skill in the art at the time of invention to have protected against barrier violating (or biochemically impossible) pathways in the method of EDWARDS by using constraints which allow for only biochemically feasible pathways, as taught by SCHILLING, where the motivation would have been to constrain flux analysis to be both feasible and biochemically meaningful, as taught by SCHILLING (p. 4195). It would further have been obvious to have used the binary variables of SCHILLING in the linear programming computations of EDWARDS where the motivation would have been to facilitate vector transformation in the method, as taught by SCHILLING (p. 4195, right column).

Applicant's arguments filed 9/14/04 have been fully considered but they are not persuasive. Applicant argues that as EDWARDS does not teach or make obvious the claimed method and system, and SCHILLING does not remedy the argued lack of EDWARDS, the claims are allowable. In response, the examiner maintains that EDWARDS does teach an FBA method for modeling cellular metabolism comprising qualitative regulatory and kinetic constraints, as set forth above. In response to the argument that EDWARDS does not teach logic constraints, it is noted that SCHILLING teaches constraining a reaction set to those which are biochemically feasible, as set forth above. As it would be illogical to include reactions which are biochemically "unfeasible" or impossible, SCHILLING's teaching is inherently one of applying logic constraints, thus the examiner maintains that the combination of EDWARDS and SCHILLING makes obvious the claimed methods and system.

Allowable Subject Matter

Claim 29 is allowed. Claim 28 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter: While the prior art of EDWARDS teaches inclusion of DNA experimental data in his FBA method of modeling cellular metabolism, as set forth above, none of the prior art teaches or fairly suggests *differential DNA microarray* experimental constraints.

Conclusion

Claims 1- 8, 10-16, and 19-27 are rejected; claims 9 and 17-18 are withdrawn.

Claim 28 is objected to; claim 29 is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in

this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37

CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later

than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Marjorie A. Moran whose telephone number is (571)

272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-

6; Fri 7-1 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marjorie A. Moran
Primary Examiner
Art Unit 1631

12/13/04